Human Genome Project

THE HUMAN GENOME PROJECT is the largest organized cooperative effort ever to be undertaken in the biologic sciences. The goal is to determine the DNA sequence of the entire human genetic program—to map and sequence every gene in the body. The complement of DNA in each cell of the body comprises about 50,000 to 100,000 functional units or genes encoded by an alphabet that has only four letters: A, adenine; C, cytosine; G, guanine; and T, thymine. About 3×10^9 letters, however, are strung together. Thus, if the linear sequence of our DNA were printed out, it would require the equivalent of nearly 100 volumes of a telephone directory to display this information. Our current understanding is that only 3% to 5% of this DNA actually codes for functional proteins that appear in some cell of the body at some stage of development. The purpose of much of the remaining DNA is as yet unclear.

Many scientific and technical problems must be overcome before the goals of the project are realized. Methods to locate individual functional genes by "mapping" techniques must be refined and made efficient, and economical procedures for sequencing must be developed. Given likely improvements in such technology, this program is feasible, but only at great cost and only with many participating laboratories cooperating in the effort.

One of the first areas affected will be an enhanced ability to diagnose and treat genetic diseases. Recent discoveries about the molecular basis of common pediatric conditions such as cystic fibrosis, Duchenne muscular dystrophy, retinoblastoma, myotonic dystrophy, and the fragile X syndrome, to name but a few, are among the early disorders to yield their secrets. We have already seen the development of rapid DNA-based tests that facilitate accurate prognostic information for these and other diseases. With more than 4,000 distinct genetic diseases known, there is a long way to go. Perhaps more important, completion of the project will allow us to identify innumerable heretofore-unknown genes and permit us to study their functions and roles in normal and pathologic processes.

Mapping the complete human DNA sequence is not an end in itself, but rather a tool to be used in concomitant and subsequent investigations. Understanding which of our genes is active and involved in development processes, oncogenesis, the response to infection, and autoimmunity will permit the design of rational interventional strategies to deal with birth defects, cancer, and many other disorders both inherited and acquired. Although the biotechnology revolution has already produced a host of new therapeutics, this number can be expected to increase by orders of magnitude using this new genomic information.

Another likely benefit of research is in the area of disease prevention. Advances in human genetics are likely to identify inherited risk factors for disorders that appear in adult life following exposure to environmental insults. A knowledge of which persons have an increased chance of common diseases of adulthood developing may permit targeted interventions that prevent or ameliorate such situations.

There are many ethical and social issues raised by the human genome project. These include concerns of genetic discrimination, the lack of availability of health care insurance for people at high risk, confidentiality of testing information, and the allocation of scarce resources. It seems certain, however, that much good will come from this work. Pediatrics will be among the medical specialties to benefit earliest and most prominently.

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Sleep Positioning and the Sudden Infant Death Syndrome

INFANTS' SLEEP POSITION has been a topic of little interest until recently. Advice from physicians and nurses to parents about sleep position has been based on scant data and thought to be of minimal clinical importance. The sudden infant death syndrome (SIDS) is the sudden, unexpected death of an apparently healthy infant that remains unexplained after a complete postmortem investigation, including an autopsy, examination of the death scene, and review of the case history.

Over the past 15 years, published reports have associated prone sleeping with an increased incidence of SIDS. Based on these reports, physicians in the United Kingdom and New Zealand have recommended that all healthy infants should sleep in a nonprone position. The question that practicing physicians and nurses in the United States must ask is, "How good are the data that prone sleeping is associated with SIDS?"

The American Academy of Pediatrics recently convened a task force to answer this question. The task force concluded that the data are convincing and furthermore stated that "no reports showed an advantage to the prone position with regard to SIDS incidence and there are no data proving, or even strongly suggesting, that sleeping in the lateral or supine position is harmful to the normal infant."

Since 1965, 25 studies have been published that considered the relationship between sleep position and SIDS. Most of these studies involved retrospective interviews after an infant died of SIDS or prospective interviews with parents of children at high risk of SIDS. Most of these studies had methodologic limitations and were conducted in countries with infant care practices and other SIDS risk factors that differ from those in the United States. Only 11 of these 25 studies used acceptable criteria for the definition of SIDS, included adequate control groups, and produced sufficient data.

These 11 studies were grouped into 3 study designs: studies examining the "usual sleep position" (7), studies examining how the infant was "last put down" before death (3), and studies asking how the infant was "found" after death (1). All of these studies showed an increased incidence of SIDS in infants who slept in the prone position, with statistical significance in all but 1 of the 11 studies. Hypotheses to explain why an infant who sleeps prone is more likely to die of SIDS include oropharyngeal obstruction, response to hypercapnia and hypoxemia, soft porous sleeping surfaces, effects on cerebral blood flow, and overheating.

There is no evidence that in healthy newborns supine or side positioning increases the incidence of aspiration or any

other serious complication. On the contrary, well-designed studies have shown that children with special needs, such as premature infants with respiratory compromise, infants with symptomatic gastroesophageal reflux, and infants with upper airway problems such as Robin's anomalad, fare better sleeping prone.

It must be emphasized to parents of healthy newborns that although associated with SIDS, prone sleeping does not cause it; and infants who insist on sleeping prone still have a low "actual risk" of SIDS. Most important, research must continue in this area so we may discern the variables that lead to this association or to disprove this association.

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Management of Intracranial and Spinal Cord Vascular Lesions in Children

MANY ADVANCES HAVE occurred in the past five years in the management of intracranial and spinal cord vascular lesions in children. These advances include improved diagnostic abilities (magnetic resonance imaging [MRI]), new interventional neuroradiologic techniques, and focused radiation therapy (radiosurgery).

The introduction of MRI has revealed vascular lesions not seen on angiography, such as cryptic vascular malformations, also known as angiographically occult vascular malformations. These lesions have been diagnosed with increased frequency because of their characteristic appearance on MRI of the mixed-signal intensity of recent and remote hemorrhage. Cryptic vascular malformations commonly produce seizures, repetitive bleeding, neurologic deficits, and, in some cases, death. The pathologic features of these malformations continue to be debated. Most can and should be removed by modern microsurgical techniques. The reported morbidity of this surgical procedure has been low even when it involves the brain stem or the motor or language cortex.

The diagnosis and management of a second disease process, intracerebral and spinal cord arteriovenous malformations, have undergone dramatic improvement. Magnetic resonance imaging can detect and localize them, often before catastrophic hemorrhages have occurred. Interventional neuroradiologic and surgical techniques can obliterate these high-risk abnormalities. Preoperative embolization in conjunction with intraoperative angiography has made "unresectable" arteriovenous malformations surgically excisable with minimal morbidity and mortality. For children with these lesions and a seizure disorder, the malformation is surgically excised in conjunction with intraoperative motor mapping and electrocorticography to remove the seizure focus. Radiosurgery has also been successfully used in children who have arteriovenous malformations in critical areas of the brain or who are thought to carry a substantial neurologic risk with surgical treatment. Both the gamma knife and linear accelerator have shown effectiveness in treating small (less than 3 cm) arteriovenous malformations. These lesions are progressively obliterated over two to three years after radiosurgery. The incidence of transient or permanent radiation damage is in the range of 2% to 4%, but complete obliteration occurs in more than 80%. To date, there is no evidence that secondary tumors are induced as the result of radiosurgery.

Combined arterial and transvenous interventional neuroradiologic techniques have dramatically improved the prognosis for infants born with a vein of Galen malformation associated with high-output congestive heart failure, previously a fatal condition.

Despite these many advances, some rare vascular malformations are not amenable to current neurosurgical therapies. These include arteriovenous malformations that diffusely permeate the brain stem and giant vascular malformations that involve an entire hemisphere. With a better understanding of the pathophysiology of vascular lesions and continued improved technologies, even these rare lesions may soon be corrected.

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Laparoscopic Surgery

LAPAROSCOPIC SURGERY is gaining acceptance among pediatric surgeons and their patients around the world. Appendectomy, cholecystectomy, Nissen fundoplication for gastroesophageal reflux, herniorrhaphy, colectomy, vagotomy, and splenectomy have all been done laparoscopically. In addition, the laparoscope can be used in children to evaluate abdominal pain of unknown cause, for treating undescended testes, and for doing biopsies of lymph nodes and tumor.

To do a laparoscopic procedure, the child must be under general anesthesia with the stomach and bladder decompressed. A retractable blunt-tipped needle is inserted through a stab wound just inside the umbilicus, and a cannula is inserted into the abdomen to fill it with carbon dioxide to a pressure of 10 to 12 torr. The procedure is then done. Laparoscopic procedures have been done on infants weighing as little as 2 kg.

Laparoscopy offers the benefits to children of decreased perioperative pain, shorter hospital stays, and an earlier return to unrestricted activity including sports. Postoperative ileus is less common after laparoscopy than after conventional operations. The decrease in length of hospital stay, however, is less pronouced in children than in adults. Children are known to recover quickly after conventional operations, and many of these procedures are generally done on an outpatient basis. The average decrease in hospital stay after a laparoscopic procedure compared with an abdominal operation is one day for an appendectomy and two days after a cholecystectomy.

Possible complications include visceral injury during trocar introduction and difficulty with ventilation when patients are insufflated with too great a pressure. Carbon dioxide absorption also poses the possibility of hypercapnia with